Avelumab in gastric cancer

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Gastric cancer (GC) is the fifth most common malignancy and the third cause of cancer-related deaths worldwide. Currently, surgery and chemotherapy remain the main therapeutic options and the prognosis of the disease is still poor in the metastatic setting. Avelumab is a human IgG1 antibody directed against PD-L1 approved for Merkel cell carcinoma and urothelial carcinoma that could be useful also for the treatment of GC. This review describes the chemical structure, the pharmacologic properties and the current knowledge of the efficacy of avelumab in the treatment of GC from the data available on the first and later phase clinical trials. The ongoing studies testing this drug either alone or in combination with other drugs are also described.

First draft submitted: 14 January 2019; Accepted for publication: 11 April 2019; Published online: 7 May 2019

Keywords: avelumab • gastric cancer • immunotherapy

Gastric cancer (GC) is the fifth most common cancer with 1,000,000 new cases in 2018 and the third leading cause of cancer-related deaths, with around 783,000 estimated deaths in 2018 (around 1/12 of cancer deaths globally) [1].

Surgery remains the main curative option for advanced GC, even if the overall 5-year survival remains very poor [2]. Moreover, perioperative and adjuvant chemotherapy – as well as chemoradiation – can improve patients' clinical outcomes. There are several chemotherapeutic drugs for GC. The main first-line treatment for this disease is the combination of platinum derivatives and a fluoropyrimidine [3,4]. Taxanes and/or irinotecan are effective second- or third-line treatment options [5–7]. Ramucirumab and apatinib are two inhibitors that block in a different way the VEGF receptor 2 (VEGFR2) that both have increased survival in pretreated GC patients [8]. Recently, trifluridine/tipiracil (TAS-102) chemotherapy showed to increase overall survival compared with placebo as third-line or later therapy for advanced GC [9]. The US FDA approved in 2017 one immunotherapeutic agent targeting programmed death-1 (PD-1), pembrolizumab, for the treatment of patients with locally advanced or metastatic GC whose tumors expressed programmed death ligand-1 (PD-L1; combined positive score ≥1) as determined by a US FDA-approved test, after having progressed to previous treatments. Approval of the drug came from the results of the KEYNOTE 059 trial [10]. In addition, nivolumab, which is a human monoclonal antibody against PD-1, showed a survival advantage against placebo in the randomized, double-blind, placebo-controlled, Phase III trial ONO-4538-12, ATTRACTION-2 [11]. This trial included 49 clinical sites of the Asian population including Japan, South Korea and Taiwan. Median overall survival was 5.26 months in the nivolumab group and 4.14 months in the placebo group. Based on these results, nivolumab has been approved in Japan. In this context, avelumab, a drug that was FDA-approved for the treatment of urothelial carcinoma and Merkel cell carcinoma has shown some positive results for the treatment of GC in early-phase clinical trials and therefore thought to be investigated in larger clinical settings [12]. For such reasons, avelumab appears to be a valid option also for the treatment of GC and there are some ongoing clinical trials that are investigating its efficacy to improve the very poor prognosis of

this disease. The purpose of this mini-review is to recapitulate the current data available for the treatment of GC through avelumab therapy. Lastly, future directions will be discussed.

The rationale for the use of checkpoint inhibitors in GC & gastroesophageal junction cancers

The evasion of immune response is a hallmark for the progression and development of cancer, including tumor escape due to the blockade of immune checkpoint pathways [13]. Key immune checkpoints proteins such as PD-1, cytotoxic T-lymphocyte antigen-4, lymphocyte activation gene protein-3, indoleamine 2,3-dioxygenase, T-cell immunoglobulin and mucin domain-containing protein 3 are overexpressed on immune cells in patients affected by GC/gastroesophageal junction cancers (GEJCs) [14–16]. Noteworthy in this context is a population of T-cells characterized by a loss of T-cell function – and therefore called exhausted T-cells – which play a pivotal role in the progression of disease [17]. PD-L1, on immune and tumor cells, and its ligand PD-1, on immune cells, have been reported to be expressed on up to 50% of GC/GEJC neoplasms and correlated with a worse prognosis [18,19]. By blocking the checkpoint proteins and hence inhibitory signals, antibodies can re-establish and promote T-cells antitumor activity [21,22]. Moreover, several GC/GEJC tumors have been reported to have a high mutational burden, especially those with microsatellite instability (MSI) [23]. Tumor mutation burden has been shown to positively correlate with better outcome in immunotherapy-treated patients [24].

On the other hand, preliminary studies eliciting an immune response in GC/GEJC have been conducted: the Bacillus Calmette-Guerin vaccine, picibanil and polysaccharide-K treatments are some examples [25]. Moreover, it is currently emerging that chemotherapy might enhance cancer immunogenicity and enhance cancer vulnerability to immune checkpoint inhibitors in the GC/GEJC treatment scenario [26].

Finally, The Cancer Genome Atlas has categorized GCs in four molecular subtypes: MSI-high, Epstein–Barr virus-positive, genomically stable and chromosomally instable [27]. Considering this molecular classification, MSI-high and Epstein–Barr virus-positive are the subtypes that may most benefit to immune checkpoint inhibitors: MSI-high for the increased number of somatic mutations secondary to the defects in DNA mismatch repair and Epstein–Barr virus-positive for the alterations secondary to the presence of oncogenic viruses and higher levels of PD-L1 expression [28]. However, EBV-positive subgroup and MSI-high account for about the 20 and 10% of all GCs, respectively.

Biologic

Avelumab (Bavencio, MSB0010718C) is an IgG1 fully human anti-PD-L1 antibody, created by EMD Serono, a business of Merck KGaA, Darmstadt, Germany, to fight tumor cells [29]. Avelumab inhibits PD-L1/PD-1 interaction in order to disinhibit T-cells and removes the suppression of T-cell activity, whose response can be assessed by evaluating the release of IFN-γ [30]. Avelumab does not modify PD-L2/PD-1 pathway permitting the continuity of PD-L2-arbitrated homeostasis [31]. Moreover, also the interaction of PD-L1 with a second inhibitory receptor, B7.1, is inhibited by avelumab; this receptor might be expressed on T-cells and antigen-presenting cells (APCs) [32]. By blocking the interaction between B7.1 and PD1 on T-cells and with PD-L1 on APCs within the lymph nodes or tumor microenvironment, avelumab might reactivate T-cells and the production of cytokines [33].

Furthermore, because of its native IgG1 crystallizable fragment (Fc) domain, avelumab conserves the ability to engage natural killer (NK) cells with the Fc-γ receptor to induce tumor-targeted antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro* [34].

This capacity to promote innate immune interactions against tumor cells makes avelumab exclusive among anti-PD-L1 or anti-PD1 antibodies in ongoing clinical trials.

Structural basis of avelumab's inhibition of PD-L1

The crystal structure of the human PD-L1 (hPD-L1) complexed with the single-chain Fv fragment (scFv) of avelumab was established at a resolution of 3.2 Å by molecular replacement. The overall structure of the complex shows that avelumab uses both light chain (V_L) and heavy chain (V_H) to tether the N-terminal domain (IgV) of PD-L1 on the side. The interaction with hPD-L1 includes five of the six complementary-determining regions (CDRs) of both V_L and V_H with a hidden area of approximately 1.856 $Å^2$. However, the binding to hPD-L1 is dominated by the V_H of avelumab by all three CDR loops and V_L contributes with partial contacts by CDR1 and CDR3 loops, allowing V_L CDR2 devoid of binding to hPD-L1. Further analysis based on structural superposition between the human PD1 (hP1)/h(PD-L1) complex and the avelumab-single-chain Fv fragment/Hpd-L1 complex

showed that the avelumab-binding epitope region on hPD-L1 overlapped with the hPD1-binding region; this result suggests that the binding of avelumab with hPD-L1 can prevent the binding of hPD1 to hPD-L1 [35]

Pharmacodynamics

The PD-1 & PD-L1 axis

The *Pd-1 gene* was initially isolated in 1992 by Ishida *et al.* using the subtractive hybridization technique and classified it in the immunoglobulin gene superfamily [36]. PD-1 is a T-cell immune checkpoint receptor that has been detected on B-cells, activated monocytes, dendritic cells (DCs) and NK cells and NK T-cells [37].

The molecule is composed of an extracellular IgV domain and an intracellular domain with buried phosphorylation sites placed on an immune receptor inhibitory tyrosine-based switch motif and an immune tyrosine-based inhibitory motif [38]. Immune tyrosine-based inhibitory motif and immune receptor inhibitory tyrosine-based switch motif tether the inhibitory phosphatase SHP-2 [39] and the former motif is required for the inhibitory activity of PD-1 on active T-cells [40].

PD-1 has shown to decrease the activity of tumor-infiltrating lymphocytes in cancer [20] and can bind to PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), which promotes T-cell anergy through the interaction with the former receptor [41]. Therefore, only the interaction between PD-L1 and PD1 promotes T-cell anergy. Successively, after the interaction between PD-L1 and PD-1, the receptor becomes inactivated. Therefore, PD-1 is a negative regulator of antitumor T-cell effector activity [42].

PD-L1 plays a pivotal role in self-tolerance, safeguarding peripheral tissues from autoimmune diseases and inflammation [43].

PD-L1 is classified as a type I transmembrane protein that consists of intracellular domains, transmembrane and extracellular domains (IgV-like domain, IgC-like domain, signal sequence) and shares 37% sequence homology with PD-L2 [44,45]. In addition, PD-L1 has been reported to be expressed on B-cells, T-cells, macrophages, DCs, pancreatic islet cells, vascular endothelial cells, lung, heart, liver and placenta [38]. While PD-L1 is mainly expressed on the surface of somatic cells following the exposure to proinflammatory cytokines [46], the PD-L2 expression is more restricted to APCs [46]. Several proinflammatory cytokines, such as IL-10, TNF-α, INF-γ, GM-CSF and VEGF, promote PD-L1 expression. PD-L1 expression caused by inflammatory cytokines in the tumor microenvironment leads to a PD-1-mediated T-cell exhaustion, thereby inhibiting the antitumor cytotoxic T-cell response [47,48].

PD-1 & PD-L1 pathway in the context of cancer

By binding its ligands, PD-1 acts as immune checkpoint under normal conditions and plays a pivotal role in silencing the immune system with the suppression of T-cells and upregulating Treg, which in turn decreases autoimmunity and enhances self-tolerance [49,50]. Once engaged with PD-L1 or PD-L2, the tyrosine phosphatases recruitment will start, leading to the blockade of the downstream activity of PI3K/Akt pathway with an inhibitory signal, and thereby to the cell cycle interruption and the T-cell activation [40,51].

A wide range of tumors such as renal cell cancer, multiple myeloma, leukemia, GC, bladder cancer, cutaneous cancer, hepatocellular cancer, glioblastoma, melanoma and breast cancer, as well as non-small-cell lung cancer show PD-L1 expression [52,53], whereas PD-1 has been notably observed on tumor-infiltrating lymphocytes [54]. Cancer cells begin to overexpress PD-L1 and PD-L2 for lowering T-cells efficiency when are attacked by the immune system; as a consequence, T-cells are silenced leading to immune escape [53]. Furthermore, by upregulation of PTEN along with the downregulation of mTOR, ERK2, S6 and phospho-Akt, PD-L1 can promote Treg cell development. Consequentially, PD-L1 will suppress the activation of T-cells as a result of the formation and the holding of Tregs [55]. Contrarly, Dong *et al.* have reported that PD1 suppress PI3K-mediated cell death in activated T-cells, leading to the downregulation of Bcl-xL and antiapoptotic proteins [41].

Furthermore, PD-1 can also suppress the T-cell receptor (TCR) acting on the inhibitory function provided by the tyrosine phosphatase SHP-2, which mediates dephosphorylation of signaling molecules downstream of the TCR [46], which is needed for the release of the stimulatory IL-2 factor, thereby making way for the cell cycle blockade and the suppression of T-cell proliferation [56].

Checkpoint inhibitors

A large number of genetic and epigenetic modifications of all cancers provide a various range of antigens that our immune system uses to recognize as 'self' or as 'non-self'. The capacity of T-cells to drive several immune

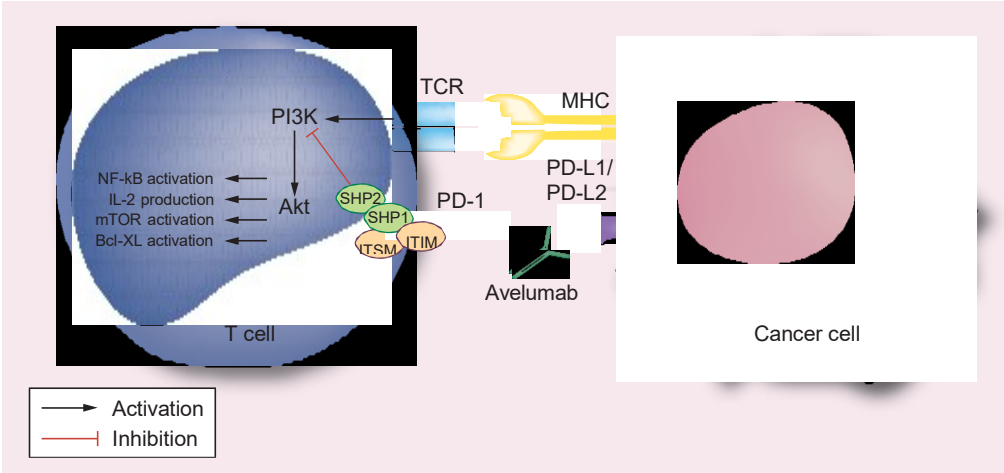

Figure 1. Mechanism of action of avelumab in the programmed death-1/programmed death ligand-1 pathway for the treatment of gastric cancer.

responses (by $CD4^+$ helper T-cells), identify and eliminate antigen-expressing cells (by $CD8^+$ effector T-cells) and distinguish peptides from all cellular compartments has made them an interesting target to pursue in order to tailor the endogenous immune system against cancer [57]. T-cell response is initiated with the TCR antigen recognition and it is regulated by immune checkpoints, which play a pivotal role in immune homeostasis maintenance [53,58]. Unrestrained immune response to pathogens or mutated/overexpressed self-antigens can cause tissue damages and autoimmune diseases. Immune checkpoints consist of costimulatory and inhibitory signals, enhancing the immune response when appropriate, but suppressing it to prevent tissue damages.

Tumors can activate inhibitory immune checkpoint in order to suppress the immune response to tumor. Therefore, the immunotherapy plans to block the suppressive immune checkpoint to re-establish the immune response against cancer (Figure 1) [59].

Several inhibitory intracellular signals are initiated through membrane receptors and their ligands are either membrane-bound or soluble cytokines. It has been shown that the overexpression of checkpoint inhibitors are found to be overexpressed in the tumor microenvironment rather than in cancer and normal tissue [48].

ADCC of avelumab

ADCC is a well-established mechanism of action for some currently used antitumoral antibodies, such as rituximab, cetuximab and trastuzumab [60]. Matching ADCC-promoting agents and tumor-targeting monoclonal antibodies (mABs) that encourage effector cells might lead to a great clinical benefit. However, engineered anti-PD-L1 IgG1 (e.g., durvalumab or atezolizumab) and anti-PD1 IgG4 antibodies (e.g., pembrolizumab or nivolumab) have been developed with a low ADCC activity, based upon a hypothetical potential of ADCC to eliminate activated T-cells [61,62]. Nevertheless, in preclinical and clinical studies, avelumab did not show any remarkable effect on the number of circulating PD-L1 immune cells or on patients' total lymphocyte count, suggesting that none immune cell subset is measurably depleted by avelumab treatment [30,63]. Thus, avelumab is the exclusive therapeutic antibody, which may exploit ADCC-mediated lysis of cancer cells and immune checkpoint inhibition simultaneously.

Pharmacokinetics & metabolism

Avelumab pharmacokinetics was assessed in patients affected by different solid tumors at doses swinging from 1 to 20 mg/kg every 2 weeks [65]. Patients who received 10 mg/kg had the mean volume of distribution at steady state of 4.72 l. Avelumab is primarily eliminated through proteolytic degradation and the circulating half-life was evaluated to be approximately 6 days, peculiarly shorter compared with the other monoclonal antibodies, possibly because of its high isoelectric point (8.9–9.3) that can raise drug uptake, distribution and clearance [66]. Forty-eight hours after avelumab infusion, immune cytokine responses were evident in some patients with a notable increase in IL-6, TNF-α and IFN-γ [66]. A dose of 10 mg/kg every 2 weeks was chosen for further developments on target occupancy and drug pharmacokinetics, since no maximum tolerated dose was identified [66].

Clinical efficacy

Phase I/Ib clinical trials

The PD-L1 inhibitor avelumab has been initially tested in two studies made of GC\GEJC patients. A Phase Ib clinical test named JAVELIN Solid Tumor trial, made of 150 patients without (1 L-mn) or with (2 L) disease progression, with locally advanced or metastatic GC\GEJC received second-line avelumab (10 mg/kg every 2 weeks) independently from the expression of PD-L1. In the 1 L-mn and 2 L subgroups, median duration of response corresponded to 21.4 months (95% CI: 4.0–NA) and 3.5 months (95% CI: 2.8–8.3) and disease control rates were of 56.7 and 28.3%, respectively. Median progression-free survival (PFS) in 1 L-mn and 2 L subgroups were 2.8 months (95% CI: 2.3–4.1) and 1.4 months (95% CI: 1.3–1.5) and overall survival (OS) of 11.1 months (95% CI: 8.9–13.7) and 6.6 months (95% CI: 5.4–9.4), respectively. The confirmed objective response rate (ORR) was 6.7% (n = 6; 95% CI: 2.5–13.9%) and the disease control rate was 28.3% [67]. A Phase I expansion cohort in Japanese patients has been investigating avelumab in patients with advanced GC\GEJC progressing to chemotherapy (JAVELIN Solid Tumour JPN) [68]. Among 21 heavily pretreated patients enrolled in the dose-expansion cohort, the ORR was 10% (95% CI: 2.8–23.7) and median OS was 9.1 months (95% CI: 7.2–11.2).

Phase III & ongoing clinical trials

A randomized Phase III clinical trial called JAVELIN Gastric 300 (NCT02625623) has been comparing the use of third-line avelumab versus chemotherapy. This clinical investigation was a randomized, multicenter, open-label, Phase III study constituted of 371 patients with advanced GC/GEJC who progressed to two lines of therapy, who were not selected for PD-L1 expression. All the patients received best supportive care (BSC) as background therapy and were stratified according to a geographic region (Asia vs non-Asia). However, this study did not meet its primary end point of improving OS, with a median OS of 4.6 versus 5.0 months (hazard ratio [HR]: 1.1 [95% CI: 0.9–1.4]; p = 0.81) in avelumab versus chemotherapy arms. Neither the secondary end points were met for PFS, with a median PFS of 1.4 versus 2.7 months (HR: 1.73 [95% CI: 1.4–2.2]; p > 0.99) nor for ORR, with an ORR of 2.2% in avelumab (n = 4; 95% CI: 0.6–5.4) versus the 4.3% (n = 8; 95% CI: 1.9–8.3) [69].

Another randomized, Phase III clinical trial made of 499 patients with GC/GEJ patients, named JAVELIN Gastric 100 (NCT02625610), has been testing the efficacy of switch-maintenance treatment. This study has been comparing avelumab versus continuation of capecitabine + oxaliplatin (XELOX) or leucovorin + 5-fluorouracil (5-FU) + oxaliplatin (FOLFOX) in patients with advanced GC/GEJC who did not progress to first-line chemotherapy. The aim of this clinical trial is to test whether avelumab can provide durable antitumor activity after tumor shrinkage and immunogenic priming obtained because of first-line chemotherapy, with less tumor toxicity burden because of the additional chemotherapy. The primary end point is to demonstrate the superiority of avelumab maintenance therapy compared with continuation of 1 L chemotherapy in terms of OS in all randomized or PD-L1-positive tumor-bearing patients. Secondary objectives include the demonstration of the superiority of avelumab versus continuation of 1 L chemotherapy in terms of PFS, ORR, safety and tolerability and quality of life [70]. Table 1 summarizes all the ongoing clinical trials testing avelumab in GC/GEJC patients.

Safety & tolerability

Avelumab is considered to be well tolerated according to the results of Phase I and II JAVELIN trials. As to the safety results of the use of avelumab from the JAVELIN phase Ib clinical trial, 17 of the patients in the dose escalation receiving avelumab did not have a dose-limiting toxicity and the maximum tolerated dose was not reached. Of the 40 patients enrolled in the dose-expansion part, 21 (52.4%) received ≥3 prior lines of therapy for the advanced disease; three of the 40 patients (7.5%) had grade 3 treatment-related adverse events (AEs) (hyponatremia, alanine aminotransferase increase and anemia) and no grade ≥4 treatment related AEs. Five of the patients (12.5%) had immune-related AE all grade 1 or 2. Therefore, avelumab had a relatively safe profile in the Japanese population with advanced GC [68]. Data from the JAVELIN II, multicenter, open-label, single-arm, Phase II trial showed that in the 1738 GC patients, grade ≥3 treatment-related adverse events (TRAEs) occurred in 177 (10.2%). The most common adverse events were fatigue (in 17 patients; 1.0%) and infusion-related reactions (in ten patients; 0.6%). TRAE leads to discontinuation in 107 patients (6.2%) and death in four patients (0.2%). Grade ≥3 immune-related adverse events (irAEs) occurred in 39 patients (2.2%) leading to discontinuation in 34 patients (2.0%). Moreover, avelumab is well tolerated with a manageable safety profile [71].

Table 1. Selected ongoing trials with avelumab in gastric cancer.

Clinical trial identifier	Study design	Intervention/s	Setting	Primary end point	Phase	Status
NCT03399071	40 participants, parallel assignment, open label	FLOT + avelumab	First-line	pCR	II	Recruiting
NCT02625610	499 participants, parallel assignment, open label	Avelumab maintenance or continuation of first-line chemotherapy oxaliplatin–fluoropyrimidine doublet after induction with	First-line maintenance	OS	III	Active, not recruiting
NCT01943461	57 participants, single group assignment, open label	Avelumab (dose escalation)	First-line	DLT	I	Active, not recruiting
NCT03475953	212 patients, nonrandomized, single group assignment	Avelumab and regorafenib	Second-line	Phase I: RPF2D Phase II: assessment of antitumor activity	I/II	Recruiting
NCT02554812	560 patients, randomized, parallel assignment, open label	Avelumab + utomilumab or PF-04518600 or PD0360324 or utomilumab + PF-04518600	Second-line	DLT	II	Recruiting
NCT03288350	55 patients, single group assignment, open label	mDCF + avelumab	Perioperative	pCR	II	Recruiting
NCT03783936	63 participants Intervention model: single group assignment, open label	mFOLFOX6 + trastuzumab + avelumab	First-line	bORR	II	Not yet recruiting

bORR: Best objective response rate; DLT: Dose-limiting toxicity; OS: Overall survival; pCR: Pathological complete response; RPF2D: Recommended Phase II dose.

Regulatory affairs

On 23rd March 2017, avelumab received the FDA approval for the treatment of metastatic Merkel cell carcinoma as a monotherapy in patients aged more than 12 years in the US and in Europe [72]. On May 2017, avelumab received the approval for patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Avelumab is administrated intravenously with a dose of 10 mg/kg over 60 min every 2 weeks [73]. Patients must undergo prior medication with antihistamine and acetaminophen to prevent infusion reactions for the first four treatments and afterward if necessary [74].

Conclusion

The stomach is susceptible to infections that trigger T-cell signaling and response leading to cancer. In fact, Capitani *et al.* showed that HP1454, a Gram-negative bacterium triggered T-cell antigen receptor-dependent signaling, Th1/Th17 inflammatory responses and lymphocyte proliferation and CXCL12-dependent cell adhesion and migration [75]. This shows how the stomach' environment is already used to mechanisms triggering the immune system and using a drug modulating such system could be a good auxiliary approach to conventional drugs. Avelumab is the most recent anti-PD-L1 antibody efficient for the Merkel cell carcinoma as it has reached FDA approval for the treatment of this disease. Despite the negative results obtained for avelumab versus chemotherapy from the Phase III clinical trial made of 371 GC patients, termed JAVELIN Gastric 300, the results from another Phase III clinical trial made of 499 patients, named JAVELIN Gastric 100, experimenting avelumab maintenance therapy versus continuation of chemotherapy could still demonstrate the survival efficacy of this recently developed monoclonal anti-PD-L1 therapy that had demonstrated its capacity of eliciting clinical responses and safety profiles in early phase clinical trials.

Moreover, there are other immune checkpoint inhibitors that have been tested in Phase III clinical trials for GC/GEJC. CheckMate 649 (NCT02872116) is a Phase III trial that has been comparing nivolumab plus ipilimumab arm versus nivolumab plus investigator choice of chemotherapy (folfox or xelos) arm versus chemotherapy alone arm. ATTRACTION 4 (NCT02746796) is a Phase II/III trial evaluating nivolumab plus chemotherapy (oxaliplatin plus either capecitabine or S-1) arm versus chemotherapy alone arm in Asian patients. KEYNOTE-062 (NCT02494583) is a Phase III clinical trial comparing pembrolizumab arm or pembrolizumab and cisplatinum/5-FU (or capecitabine) arm versus cisplatin/5-FU alone arm for treating PD-L1-positive GC/GEJC patients.

The results from the ongoing clinical trials testing avelumab and other immunotherapies are eagerly awaited to evaluate the capacity of checkpoint inhibitors to improve advanced GC/GEJC clinical outcomes. Of note, as an alternative strategy the checkpoint inhibitor could be used in combination with stimulators of T-cells' receptors. For example, nivolumab and/or ipilimumab have been tested for advanced GC/GEJC (NCT03126110) in combination with INCAGN91876 (anti-glucocorticoid-induced tumor necrosis factor receptor-related protein) versus ipilimumab alone.

Moreover, there is a need in future to have accurate predictive biomarkers that could help clinicians to decide whether patients would best respond or not to checkpoint inhibitors. Since in a large cohort of 2220 lung cancer patients in a Phase III, multicenter, open-label study showed that patients respond better to checkpoint inhibitors when they have a high tumor burden, even better than in patients with high PD-L1 [76], it might be interesting in future to test tumor burden as a predicting biomarker for the efficacy of immunotherapy in GC/GEJC.

Executive summary

Background

- Gastric cancer (GC) is the fifth most common malignancy and the third cause of cancer-related deaths worldwide.

Biologic

- Avelumab is a human IgG1 antibody directed against PD-L1 that could be useful also for the treatment of GC.
- The chemical structure, pharmacologic properties and current knowledge of the efficacy of avelumab in the treatment of GC from the data available are described.

Clinical efficacy

- The ongoing studies testing this drug either alone or in combination with other drugs are also reported.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Company review

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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• **It shows the impact the disease has in the clinical world and how important it is to find an alternative way to better treat the disease.**

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